10

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

09/757,992

To:
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ENTERED
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FEB 13 2002
FILE 200701/1062
DKT

PCT

WRITTEN OPINION

(PCT Rule 66)

	Date of Mailing *(day/month/year)*	10 JAN 2002
Applicant's or agent's file reference 200701/1062	REPLY DUE within 1 months/days from the above date of mailing	
International application No. PCT/US01/03706	International filing date *(day/month/year)* 02 February 2001 (02.02.2001)	Priority date *(day/month/year)* 02 February 2000 (02.02.2000)
International Patent Classification (IPC) or both national classification and IPC IPC(7): C12Q 1/68 and US Cl.: 435/6		
Applicant ADVION BIOSCIENCES, INC.		

1. This written opinion is the first (first, etc,) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2 (a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☒	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension. See rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 02 June 2002 (02.06.2002).

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Bradley L. Sisson Telephone No. (703) 308-0196

Form PCT/IPEA/408 (cover sheet)(July 1998)

WRITTEN OPINION

International application No.
PCT/US01/03706

I. Basis of the opinion

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☒ the description:
pages 1-43, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 44-53, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages 1-22, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE _____

☐ the claims, Nos. NONE _____

☐ the drawings, sheets/~~fig~~ NONE _____

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed."*

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 21-53

because:

☐ the said international application, or the said claim Nos. ____ relate to the following subject matter which does not require international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. ____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. ____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 21-53.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

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V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	14-18	YES
	Claims	1-13 and 19-20	NO
Inventive Step (IS)	Claims	18	YES
	Claims	1-17 and 19-20	NO
Industrial Applicability (IA)	Claims	1-20	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1, 3-12, and 19-20 lack novelty under PCT Article 33(2) as being anticipated by Ross (*Analytical Chemistry*, Vol. 69, 1997, pages 4197-4202). Ross et al., disclose a method for determining single nucleotide polymorphisms in a target nucleic acid through the combined use of nucleotide analogs that are incorporated into primer extension products and then subjected to MALDI-TOF mass spectrometry.

Claims 1-13, 19, and 20 lack novelty under PCT Article 33(2) as being anticipated by Haff et al. (US 5,885,775). Haff et al., column 2, discloses utilizing dideoxynucleotides in an amplification reaction and then subjecting the resultant amplification product to MALDI-TOF mass spectrometry so to determine point mutations.

Claims 1-13, 19 and 20 lack novelty under PCT Article 33(2) as being anticipated by Sequenom, Inc. (WO 98/20166). Sequenom, Inc., (Sequenom) disclose at length methods for determining the presence of point mutations in a target nucleic acid by subjecting the target nucleic acid to amplification and the optional use of a chain terminating nucleotide such as ddNTPs and determining whether there was a point mutation via mass spectrometry; see pages 14-17. The performance of an "electrospray" is disclosed (Figure 11; page 23, fourth paragraph).

Claims 1-17 lack an inventive step under PCT Article 33(3) as being obvious over either Haff et al. (US 5,885,775) or Sequenom, Inc. (WO 98/20166), in view of Martin (US 5,969,116). Haff et al., column 2, discloses utilizing dideoxynucleotides in an amplification reaction and then subjecting the resultant amplification product to MALDI-TOF mass spectrometry so to determine point mutations in a target nucleic acid. Haff et al., do not disclose use of a resin so to remove magnesium.
Martin, columns 41-42, discloses removing magnesium salts from a nucleotide-containing composition be use of a chromatography resin of ethyl acetate/methanol 9:1. At column 49 Martin also discloses subjecting resultant oligonucleotides to MALDI-TOF mass spectrometry.
It would have been obvious to a routineer in the art at the time the invention was made to have adapted the method of Haff so to include the step of removing magnesium salts from a nucleic acid composition ant to then have subjected the composition to MALDI-TOF mass spectrometry so to determine point mutations in the target nucleic acid. In view of the well-developed nature of the art, including the explicit teachings of performing amplification and determining point mutations through MALDI-TOF mass spectrometry analysis of the amplification product, routineer would have had a reasonable expectation of success.

Claims 1-20 meet the criteria set out in PCT Article 33(4), because the aspect of detecting single point mutations is considered to satisfy the requirement of industrial applicability.

---------- NEW CITATIONS ----------
US 5,885,775 A (HAFF et al.) 23 March 1999, see column 2, first paragraph.
US 5,969,116 A (MARTIN) 19 October 1999, see columns 41-42, and column 49.
WO 98/20166 A2 (SEQUENOM, INC.) 14 May 1998, see entire document.

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VI. Certain document cited

1. Certain published documents (Rule 70.10)

Application No Patent No.	Publication Date *(day/month/year)*	Filing Date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
US 6,277,573 B1	21 August 2001 (21.08.2001)	06 April 1999 (06.04.1999)	None

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

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VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to adequately enable practice of the claimed invention because: The aspect of shearing the mixture of amplification product prior to detection renders an accurate determination of any point mutation most improbable if not impossible. As presently worded, the method of claim 18, and by default, claims 1 and 3 from which it depends, requires that the amplification product be sonicated whilst in an apparent desiccated state. The aspect of sonicating any nucleic acid residue speaks directly to the shearing of the nucleic acid in a random manner. The claims are considered to encompass the presence of any length of amplification product as well as any length and heterogeneity of amplification product. To subject such a mixture, or even the sonication of a single product, in a random manner would undoubtedly result in a series of fragments. The disclosure does not set forth a repeatable procedure whereby a routineer in the art would be able to determine if there was a shift in mass, much less a determination of a point mutation in the target nucleic acid.

Claims 1, 3, and 18 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not enabled as required under PCT Rule 5.1(a) for the reasons set forth in the immediately preceding paragraph.

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Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

TIME LIMIT:
The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.